REMARKS

Reconsideration and withdrawal of the rejections to the applications are respectfully requested in view of the amendments, remarks and enclosures herewith.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 39 to 59 are now pending. Claims 1-38 have been canceled, and new claims 39-59 have been added herein, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103, or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Support for the amendments to the claims can be found in the claims as originally filed. Specifically, claim 39 has been amended to incorporate the language of previous claim *5,* as well as functional language to specify that the P3 sub-unit polypeptide or peptide fragment is "capable of co-operating with at least one a-sub unit of voltage-gated sodium channels to form an active sodium channel". This feature is disclosed at lines 27 to 29 of page 5 of the specification as filed. In addition, this claim (as well as a number of others) now specifies that the amino acid identity is over the entire length of the sequence referred to. Claims 40 to 43 correspond to previous claims 10, 12, 11 and 13 respectively, while claim 44 is a combination of previous claims 1 and 4, together with the functional language referred to above. Claims 45 to 48 correspond to previous claims 6, 8,7 and 9 respectively, while claim 49 is an amended version of previous claim 14, incorporating a functional restriction and reference to SEQ ID Nos: 3 and 4. Claims 50 to 59 correspond respectively to previous claims 15, 16, 17, 20, 24, 25, 26, 27, 28 and 29, with a number of minor changes to claim dependency.

II. THE OBJECTIONS TO THE APPLICATION ARE OVERCOME - ACCEPTANCE OF THE REVISED SEQUENCE LISTING IS REQUESTED

The application was objected to as failing to contain the appropriate sequence identifiers in either the drawings themselves or in the brief description of the drawings. Additionally, claim 14 was objected to as referring to specific nucleotide sequences by accession number instead of SEQ ID NO.

It is respectfully submitted that the amendments to the application herein have rendered the objections moot. Specifically, the descriptions of Figures 1 and 4 have been amended to include the appropriate sequence identifiers. Furthermore, a revised sequence listing has been enclosed herewith which includes those sequences previously incorporated into the present application by reference and referred to only as "SEQ ID NO: 876 in WO 98/45435" and "accession number AA685538". Accordingly, these sequences are also now identified in the claims by the proper sequence identifier.

In accordance with this revision to the sequence listing, Applicants respectfully request acceptance of the enclosed computer readable and paper copy of the Sequence Listing.

It is respectfully asserted that this application now fully complies with the requirements for applications containing sequence listings as set forth in 37 C.F.R. § 1.821 to § 1.825. The Statements required by 37 C.F.R §1.821(f) and (g) are set forth below.

The undersigned hereby states that this submission, filed in accordance with 37 C.F.R. §1.821(g), does not contain new matter. Pursuant to 37 C.F.R. §1.821(f), the undersigned hereby states that the content of the paper and computer readable copies of the Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), respectively, are the same.

Accordingly, reconsideration and withdrawal of the objections to the disclosure are respectfully requested.

III. THE CLAIM REJECTIONS UNDER 35 USC §§ 101 AND 112 ARE OVERCOME

Claims 1-3, 10-14, 16, 20 and 24-29 were rejected under 35 U.S.C. §101, because the claims are allegedly not supported by either a specific and substantial utility or a well established utility. The rejection is respectfully traversed.

The Office Action alleges that none of the uses for the claimed polypeptides, as described in the specification, are specific and substantial. Applicants respectfully disagree.

Contrary to the assertions in the Office Action, the specification clearly demonstrates that the polypeptides encoded by the nucleic acids are useful as targets of drugs capable of modulating voltage-gated sodium channels as well as in the identification of modulators of such channels, these drugs being capable of treating a number of diseases specifically identified in the application as being associated with the β3 sub-unit. For example, at lines 4 to 5 of page 4 of the specification, the application as filed discloses that the β3 sub-unit is involved in pain, epilepsy, stroke, ischemia and heart disease. Furthermore, the Examiner's attention is respectfully directed towards the second paragraph of page 6, which states:

> The inventors have thus demonstrated that the β3 sub-unit of the invention is involved in the regulation of the sodium currents induced by the voltage-gated sodium channels. They have also determined that the β3 sub-units of the invention may be valuable targets for drugs capable of up regulating or down regulating the activity of voltage-gated sodium channels, in particular drugs designed for preventing or treating pain, epilepsy (typically febrile seizures and generalized epilepsy), stroke, ischemia, heart disease, Jacobsen Syndrome, Familial Nonchromaffin Paraganglioma, Phenylketonuria due to PTS deficiency and Charcot Marie Tooth disease. Appropriate modulation of β3 may therefore be taken into account in the treatment of such diseases.

Clearly, the present application does, in fact, provide sufficient disclosure of the specific diseases associated with β3 sub-unit. Combined with the disclosure that the polypeptides may be used to screen for modulators to treat such diseases, Applicants respectfully assert that there is clear utility in the polypeptides (and therefore nucleic acids encoding them), which utility is both specific and substantial. In addition, the utility is credible, as there is no reason to doubt the statements provided in the specification of the utility of the β3 sub-unit polypeptides.

The Examiner's attention is respectfully directed to those documents enclosed herein which were published subsequent to the priority date of the present application and which support the utility disclosed in the present application as filed. These documents comprise three journal publications (Shah *et al.*, 2000, European Journal of Neuroscience 12, 3985-3990, *Shah et al.*, 2001, Neuroscience Letters 309, 1-4 and *Maier et al.*, 2004, Circulation 109, 1421-1427) as well as a page headed "Support for pain claim" comprising additional experimental data.

Shah *et al.* (2000) discloses that β3 sub-unit is expressed preferentially in sensory neurons, indicating that it is involved in the perception of pain. This is confirmed by expression studies which show that β3 sub-unit expression is up regulated in a chronic constriction injury model of neuropathic pain. The Examiner's attention is respectfully directed to Figure 4, as well as to the third paragraph of the right-hand column of page 3988. In addition, the third complete paragraph of the left-hand column of page 3989 states clearly that "... increased ectopic firing of sensory neurons in neuropathic pain is thought to arise from increased expression of voltage-gated sodium channels in sensory cells... ." Furthermore, the last sentence of the fifth complete paragraph of that page states that "... the up regulation of β3 allows α3- β3 coupling in DRG neurons under hyperalgesic conditions with resulting increased excitability of these neurons".

It is therefore clear from Shah *et al.* (2000) that β3 sub-unit is involved in the perception of neuropathic pain, and therefore that the use of β3 sub-unit in screening for modulators as pain therapies is specific, substantial and credible.

Shah *et al.* (2001) shows that β3 sub-unit expression is up regulated in sensory neurons following streptozocin induced diabetic neuropathy in rat (see Figure 1 as well as the first and second complete paragraphs of the right-hand column of page 2). Lines 5 to 7 of the second complete paragraph of the right-hand column of page 3 of this document states clearly that "... β3 is known to associate with sodium channel a sub-units thought to be important in pain pathways such as PN3 and α3 ...". Thus, Shat *et al.* (2001) also supports the specific, substantial and credible utility disclosed in the application as filed for the β3 sub-unit.

Further support is provided by the additional experimental data in the page headed "Support for pain claim". The inventors used the nucleic acid sequence of β3 sub-unit, disclosed for the very first time in the present application, to create transgenic knock-out animals, which are deficient for expression of β3 sub-unit. These animals were then subjected to a standard "tail-flick test", which assesses the sensitivity of these animals to noxious stimuli (in this case heat-induced pain). The graph on the left-hand side shows that transgenic animals which do not express β3 sub-unit show less sensitivity to noxious stimuli, indicating clearly that loss of β3 sub-unit results in concomitant loss in pain sensitivity. β3 sub-unit is therefore clearly demonstrated to be involved in the perception of pain. The inventors also demonstrate on the right-hand panels that β3 sub-unit is expressed in small fibers which colocoluse with IB4 pain

sensing C-fiber neurons, further supporting the credibility of the stated utility for the β3 sub-unit. Applicants would be willing to submit a declaration attesting to this data should the Examiner find that such a declaration would be beneficial.

Finally, the publication of Maier *et al.* (2004) supports a role for β3 sub-unit in ischemia and heart disease. Maier *et al.* shows that cardiac sodium channels are composed of $Na_v1.1$, $Na_v1.3$, and $Na_v1.6$ plus β1 or β3 sub-units in the transverse (t-) tubular system (see lines 4 to 6 of the left-hand columnn of page 1422, Figure 3 and the first and second sentences of the first complete paragraph of the right-hand column of page 1425). The authors conclude at lines 37 to 39 of the left-hand column of page 1426 that "... sodium channels in transverse tubules may function in co-ordinating and synchronising the conduction of the action potential from the cell surface of the myocyte into the interior via the transverse tubules". Accordingly, the β3 sub-unit is clearly shown by Maier *et al.* (2004) to be involved in heart function, particularly with reference to the first sentence of the first complete paragraph of the right-hand column of page 1421, which states that "alterations in sodium channel expression and function are known to have severe effects on excitability. In the nervous system, mutations in sodium channel α and β3 sub-units cause epilepsy and febrile seizures".

Accordingly, both the teaching of the specification at the time of filing, as well as the teachings of the enclosed, peer-reviewed articles that were published following the priority date of the present application, clearly demonstrate that the invention as currently claimed as substantial and specific utility. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §101 are respectfully requested.

Claims 1-3, 10-14, 16, 20 and 24-29 were rejected under 35 U.S.C. §112, first paragraph, because the alleged lack of utility renders the claims non-enabled and prevents one of skill in the art from knowing how to use the claimed invention. The rejection is respectfully traversed.

As clearly indicated above, the present invention does have a substantial, credible, utility. Furthermore, the amendments herein have the result that sequences identified within the claims are no longer identified by name only, but rather by specific sequence identification numbers. Furthermore, contrary to the assertions in the Office Action, it is well within the skilled person's ability and knowledge to make sequences that have a specific percent identity to a reference sequence. For example, the skilled person could make reference to textbooks in the area of molecular biology, such as Sambrook *et al.*, as cited in the application, for guidance in preparing

such sequences. Furthermore, the claims as amended require that the nucleic acids encode polypeptides having a specific function, and the specification clearly discloses that function as well as methods for assaying for that function (see Examples 6 and 7 on pages 45 to 48 of the specification as filed).

The Office Action also alleged that claims 10 and 11 were drawn to isolated nucleic acids defined only be sequence identity to SEQ ID NO: 4 or a portion thereof, with no requirement that the nucleic acids encode a protein with a particular function. As described above, the claims as amended herein now require that the nucleic acids encode polypeptides having a specific function, such that this rejection, for this reason alone, is moot. However, the Office Action also stated that there was no guidance in the specification to assist one of skill in the art when modifying SEQ ID NO: 4. Applicants respectfully disagree.

Pages 15 to 19 of the application as filed describe in great detail the two dimensional and three dimensional structure of the β3 sub-unit. These passages also include important information as to the regions within these structures which are believed by the inventors to be crucial, for β3 sub-unit activity. Clearly the skilled person would have no difficulty in applying these teachings to the design of sequences falling within a certain identity percentage of a reference sequence. Thus, one would know that in order to make such sequences, they should modify regions of the protein which are shown to be not essential for activity, or not conserved between sequences of different species. Armed with this knowledge, the skilled artisan could easily mutate the β3 sub-unit at the regions which one is guided to, using methods they are well acquainted with, to obtain such related sequences. Furthermore, a skilled person would not deliberately set out to pursue embodiments that would fail, but would have a clear motivation to seek out and make those embodiments that would work. Accordingly, the skilled artisan would rely on their own knowledge and the disclosure of the application to make such modifications of the sequences.

The Office Action also objects to the use of the term "a pair of amplification primers" as guidance is allegedly "not given as to what constitutes an amplification primer." Applicants respectfully assert that the term "amplification primer" is a term which is well known in the art, such that there is no necessity to provide additional guidance as to the nature of such primers. One of skill in the art would recognize such a term and would be easily able to identify suitable

amplification primers. For example, a skilled person would know clearly that this would very much depend on the particular portion (or whole) of the β3 sub-unit that they intend to amplify.

The Office Action also rejected claim 28 due to the use of the term "recombinant host cell" which the Office Action deemed to include cells in a human body, such that the present invention would therefore include gene therapy. Applicants disagree with this interpretation, but have utilized the term "isolated recombinant cell" in the currently pending claims to avoid this interpretation.

For all of the reasons described above, the present claims are clearly enabled. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Claims 1-3, 10-14, 16, 20 and 24-29 were rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. The rejection is respectfully traversed.

The Office Action states that the claims do not recite any specific sequence, but rather only the name of a gene. As stated above, the amendments to the claims herein have the result that sequences identified within the claims are no longer identified by name only, but rather by specific sequence identification numbers. Accordingly, the rejection is now moot.

The Office Action also states that claims 12 and 13 require two specific residues, but that they do not require that the nucleic acids comprise the entire sequence between the residues referred to as the starting and end points. The amendments herein have adopted the language suggested in the Office Action, such that the rejection is now moot.

The final portion of the written description rejection indicated that "the instant disclosure of two nucleic acid sequences cannot support description of the entire genus of polynucleotides." Office Action at 9. The Office Action continues to state that "[a]n adequate written description of a DNA or protein, 'requires a precise definition, such as by structure, formula, chemical name or physical properties'." Office Action at 9. It is respectfully submitted that the amendments herein have overcome the written description rejection.

The claims are now directed towards a purified or isolated nucleic acid which encodes a polypeptide having at least 80% amino acid identity with the β3 sub-unit polypeptide of the amino acid sequence of SEQ ID NO: 2 over the entire length of the sequence of SEQ ID NO: 2, or with a peptide fragment thereof, or a sequence complementary thereto, said β3 sub-unit

polypeptide or said peptide fragment which co-operates with at least one α-subunit of voltage-gated sodium channels to form an active sodium channel. Accordingly, the claims now recite both a specific sequence identifier, and additionally recite a required functionality. Consequently, the nucleic acid sequences and/or proteins of the present invention are now specifically defined and adequately described by the present specification. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

IV. THE ART REJECTIONS ARE OVERCOME

Claims 14, 16 and 24 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Fleishmann et al. (U.S. Patent No. 6,294,328).

Claims 14, 16, 20, 24 and 26-29 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Lovenberg et al. (U.S. Patent No. 6,723,841).

Claims 14, 16 and 24 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by GenBank Locus D44825.

Claims 1-3, 10, 16, 20, 24 and 27-29 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Stratagene random primers, (1991 catalog, p. 66).

Claims 1-3, 10, 14, 16, 24 and 25 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fleishmann et al. in view of Brown et al. (U.S. Patent No. 5,807,522) or alternatively over Lovenberg et al. in view of Brown et al., or alternatively over D44825 in view of Brown et al., or alternatively Stratagene in view of Brown et al.

The rejections are traversed and will be addressed simultaneously.

Initially, it is respectfully submitted that for a Section 102 rejection to stand, the single prior art reference must contain all of the elements of the claimed invention, *see Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), and, the single prior art reference must contain an enabling disclosure, *see Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990).

It is also well-settled that as to a rejection under 35 U.S.C. §103, there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as

stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applying the law to the instant facts, it is respectfully submitted that the instant invention is not anticipated or made obvious by any of the cited references, *inter alia*, because none of the references contain a teaching of all of the elements of the instant claims. And, it is respectfully submitted that the instant invention is not rendered obvious by any of the cited references, either alone or in any combination thereof, as none of the references provide a teaching or suggestion of all of the elements of the instant claims, *inter alia*.

The amendments to the claims herein have incorporated functional language into the independent claim to specify that the P3 sub-unit polypeptide or peptide fragment is "capable of co-operating with at least one a-sub unit of voltage-gated sodium channels to form an active sodium channel". Furthermore, it is now specified that any claimed amino acid identity is over the **entire** length of the sequence referred to.

At the very best, the sequences presented in the cited references are merely "expressed sequence tags" (Genbank Locus D44825) or small and insignificant portions of sequences encoding other, completely unrelated, polypeptides which just happen to match the present sequences over a very limited range (US 6,2994,328 and US 6,723,841), **not over the entire length of the sequence** as is required by the present invention. None of these documents disclose a polynucleotide which encodes a polypeptide which co-operates with at least one α sub-unit of voltage-gated sodium channels to form an active sodium channel, which functional requirement is clearly set out in claims 39 and 49.

Accordingly, the claims are novel over the cited references. Similarly, the subject matter of the claims is inventive over the cited at, as none of these documents remotely suggests the function identified for the very first time by the inventors. Consequently, reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102 and 103 are respectfully requested.

V. THE DOUBLE PATENTING REJECTIONS ARE OVERCOME

Claims 1-3, 10-14, 16, 20 and 24-28 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 10-13, 17, 20 and 24-28 of copending Application No. 09/936,680.

Applicants respectfully request that the provisional double patenting rejection with held in abeyance until such time as allowable subject matter is determined in either the present application or in copending Application No. 09/936,680, at which time Applicants respectfully request that the rejection be made in the application still pending in view of the patent issuing from either of these applications.

VI. INFORMATION DISCLOSURE STATEMENT

The Examiner's attention is respectfully drawn to the documents listed on the accompanying PTO Form 1449. Copies of the documents are enclosed.

The filing of this Information Disclosure Statement is not an admission that the documents identified herein constitute prior art to the present application. Entry of this Information Disclosure Statement is respectfully solicited, and the Examiner is requested to initial and return a copy of the PTO-1449 to the Applicant. As this Information Disclosure Statement is being filed after the mailing of a first office action on the merits, the Commissioner is hereby authorized to charge any fee required for consideration of this Information Disclosure Statement, or any other fee occasioned by this paper, or to credit any overpayment in fees, such may be charged or credited to Deposit Account No. 50-0320.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner and his supervisor, is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In light of the remarks, amendments and enclosures herewith, the application is in condition for allowance. Reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance, is respectfully requested.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorney for Applicants

By: _____

Thomas J. Kowalski
Reg. No. 32,147
Angela M. Collison
Reg. No. 51,107
(212) 588-0800